Association between obesity and gallbladder cancer

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1. ABSTRACT

Obesity has become a global health issue because of its increased morbidity and mortality, and a close association with at least 20 different cancers. Clinical and epidemiological studies have suggested that obesity and overweight are positively related with the risk of GBC. Gallbladder cancer (GBC) is a relatively infrequent but highly lethal neoplasm. Obesity may disturb lipid and endogenous hormones metabolism, affect gallbladder motility, increase the risk of gallstones, and thus plays a role in GBC. Control of obesity through measures such as lifestyle modification, healthy diet, and regular exercise may prove useful in the prevention of GBC.

2. INTRODUCTION

Worldwide, obesity is not only an escalating health threat but it poses considerable impact on the global economy and may have serious psychosocial consequences. Body mass index (BMI) is the most widely used measure of obesity due to its high correlation with fat mass accumulation and obesity-related disease risk. According to the WHO definition, a BMI $\geq 25 kg/m2$ indicates overweight, while a BMI $\geq 30 kg/m2$ suggests obesity (1). In addition to damaging multiple organs and systems, obesity increases the cancer risk of many organs by 1.5-3.5 fold compared with normal-weight subjects (2), such as adenocarcinoma of the oesophagus, postmenopausal breast cancer, colon, kidney, prostate and thyroid cancer. (3, 4, 5,

6, 7). Gallbladder cancer (GBC) is the most common biliary tract tumor with a late manifestation and poor prognosis. Cholelithiasis, porcelain gallbladder, gallbladder polyps, endogenous and exogenous estrogens, and bacterial infections have been recognized as common risk factors for GBC (8). Studies in the recent years have demonstrated a close link between obesity and GBC (9, 10). In this article, we summarize the clinical and experimental data on the role of obesity in GBC.

3. EPIDEMIOLOGY OF OBESITY

The prevalence of overweight worldwide has been increasing substantially over the past two decades. According to data from National Health and Nutrition Examination Survey (NHANES) in 2005 to 2006, approximately 67.3% of the US population was overweight or obese and for the first time the prevalence of obesity (35.1%) exceeded that of overweight (32.2%) (11). The increasing BMI and increasing obesity prevalence are affecting the entire population of men and women of all ethnic groups, of all ages, and of all educational and socioeconomic levels (12, 13). The WHO estimates that in 2008, 1.5 billion adults were overweight, and of these over 200 million men and nearly 300 million women were obese. Overall, more than 10% of the world's adult population was obese (1). It is predicted that by 2015, approximately 2.3 billion adults will be overweight and at least 700 million will be obese (14). The most worrisome fact is that obesity is also increasingly common in children. The WHO had predicted that in 2010, over 42 million children under the age of five were overweight globally, of these close to 35 million are living in developing countries and 8 million are in developed countries (1).

4. EPIDEMIOLOGY OF GBC

GBC is relatively rare and has traditionally been associated with a poor prognosis because of late diagnosis and few effective treatment options. Patients with GBC usually have few symptoms or signs but can deteriorate rapidly due to the development of metastatic disease (15). According to the latest data, GBC is the sixth most common gastrointestinal malignancy in terms of incidence and the 20th most common in terms of cancer-related death in the USA (16, 17). The 5-year relative survival rate is only 16.5 per 100,000 persons (2001-2007) (18). In 2008, 9,250 new cases of GBC and other extrahepatic biliary duct cancers were reported in the USA, and the estimated age-adjusted incidence of GBC was 1.2 per 100,000 persons (male is 0.8, female is 1.5) from 2004 to 2008 (16, 17). GBC exhibits marked geographic and ethnic variation. Worldwide data suggest that most of the top 50 locations for GBC have an incidence of approximately 3.0 to 4.0 per 100,000. The highest GBC incidence rates among men and women have been reported in Chile (Valdivia, 12.3-27.3 per 100,000 populations, respectively) (19, 20). GBC is relatively uncommon in China, however the incidence of biliary tract cancer rose by more than 100% in Shanghai between 1972 and 1994 (21).

In a Norwegian study involving over two million people and 1,715 cases of GBC, it was showed that overweight and obese women had markedly higher risk of GBC compared with normal subjects. Compared to women with a BMI of 18.5-24.9 kg/m2, the relative risk (RR) for GBC in women with a BMI of 35.0-39.9 kg/m2 was 2.56, and in women with a BMI of ≥40.0 kg/m2, the RR for GBC was 2.77 (22). In a large cohort study from the USA, the reported RR for GBC in obese white men was 1.7 (95% CI: 1.1-2.6) (23). Similar data were reported in several other clinical studies and meta-analysis reviews (24-26). In a meta-analysis involving three case-control studies and eight cohort studies with a total of 3,288 cases, the RR for GBC was reported to be 1.15 and 1.66 among overweight and obese subjects, as compared with individuals of normal weight. The association between obesity and GBC appears to be stronger in women than in men. Data from the United Kingdom have showed that BMI≥30 kg/m2 is a threshold with a 1.5 times higher risk of both cholangiocarcinoma and GBC, as compared to those with a BMI of 25 kg/m2 (27). Similarly, a case-control study in Poland found that the risk of GBC was positively associated with increased total calorie intake with an odds ratio (OR) of 2.00 (1.10-3.70) (28).

An association between obesity and GBC has also been confirmed in a recent population-based case control study in China (29). The study recruited 627 patients with biliary tract cancers (368 with GBC, 191 with bile duct cancers, and 68 with ampulla of Vater cancers) and 959 healthy subjects. The study showed that in the individuals of general and abdominal obesity (measured by BMI and waist-to-hip ratio, respectively), including obesity in early adulthood, adults with a BMI≥25.0 kg/m2 had a 1.6-fold higher RR of GBC than normal subjects (95% CI 1.2-2.1). This correlation was also seen among subjects without gallstones, suggesting that the effect of obesity on GBC may not be mediated by gallstones (30).

5. OBESITY AND GBC: POSSIBLE MECHANISMS

5.1. Insulin resistance, hyperinsulinemia, and insulin-like growth factors (IGF) increase the cancer risk

Although the biological mechanisms of how obesity may promote carcinogenesis are not firmly defined, some plausible mechanisms have been suggested, including insulin resistance and resultant chronic hyperinsulinemia, increased production of insulin-like growth factors (IGF), and increased bioavailability of steroid hormones (2). Insulin is the core component in metabolic syndrome. The tumorigenic effects of insulin could be directly mediated by insulin receptors (IR) in the (pre)neoplastic target cells, or might be due to related changes in endogenous hormone metabolism, secondary to hyperinsulinaemia. Insulin promotes the synthesis and biological activity of IGF-I and has effects on the synthesis and biological availability of the sex hormones, including androgens, progesterone and oestrogens(31).

Insulin resistance manifested by increased hepatic glucose release and reduced whole body glucose disposal, develops as a metabolic adaptation to increased
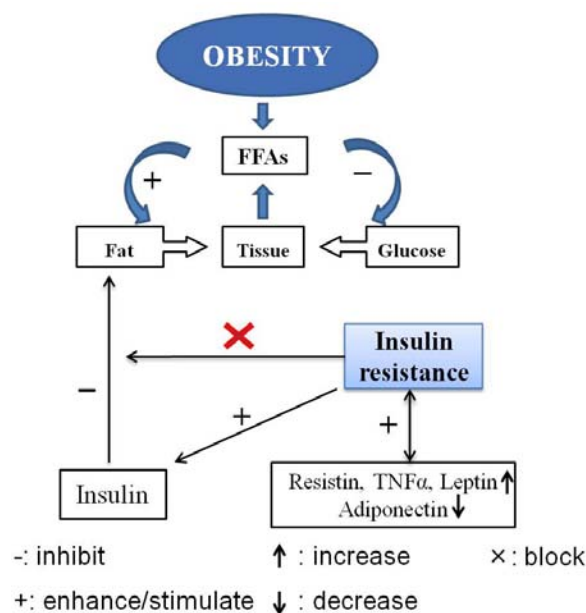
Figure 1. FFAs released by the adipose tissue increase fat storage and oxidation by liver, muscle and other tissues for energy production. This, however, may lead to a reduced capacity of these tissues to absorb, store and metabolize glucose. The suppression of lipolysis by insulin is inhibited in insulin resistance, leading to an increased release of FFAs. Increased circulating insulin level is associated dysregulation of adipose derived hormones (or adipokines) such as adiponectin, leptin, tumor necrosis factor-alpha (TNFα), and resistin, which in turn can give rise to more insulin resistance.

circulating levels of free fatty acids (FFAs) constantly released by the adipose tissue, especially the visceral fat. Increased FFAs levels have a deleterious effect on insulin uptake by the liver and force liver, muscle and other tissues to shift towards increasing storage and oxidation of fats for energy production, which is associated with a reduced capacity of these tissues to absorb, store and metabolize glucose. In turn, the suppression of lipolysis by insulin is inhibited in insulin resistance, leading to an increased release of FFAs, accordingly setting up a vicious cycle of events (32). Increased circulating insulin level has been reported to associate dysregulation of adipose derived hormones (or adipokines) such as adiponectin, leptin, tumor necrosis factor-alpha (TNFα), and resistin. Alterations of these molecules may contribute to tumorigenesis and tumor invasion, as recently reviewed (33, 34). Of note, increased release of FFAs, resistin and TNFα, leptin and reduced production of adiponectin give rise to more insulin resistance. To prevent an excessive rise of blood glucose levels, insulin resistance is generally compensated by increased pancreatic insulin secretion, leading to hyperinsulinemia (35) (Figure 1).

IGF-I is a peptide hormone that has a molecular structure very similar to that of insulin and could regulates cellular proliferation in response to available energy and

nutrients from diet and body reserves. Over 80% of IGF-I in the circulation is bound to IGF binding protein (IGFBP)-3, whereas most of the remainder is bound to at least five additional binding proteins (IGFBP1, IGFBP2, IGFBP3, IGFBP4, IGFBP5 and IGFBP6). In normal cells, IGFBPs bind to IGF-I with high affinity, effectively sequestering IGF-I and inhibiting pathway activation through interaction with the IGF-I receptor (IGF-IR). Chronic hyperinsulinemia reduces the hepatic production of IGFBP-1 and IGFBP-3, result in more unbound IGF-I that is free to interact with IGF-IR, thus increase the quantity of bioavailable IGF-I (36). Insulin and IGF-I signal through binding to the insulin receptors (IRs) and IGF-IR, respectively, promote cellular proliferation and inhibit apoptosis in many tissue types. These effects might create a cellular environment that favors tumor development (37).

The primary cell survival pathway activated in the IGF-I axis is the phosphatidylinositol 3 kinase /Akt (PI3K/Akt) signaling pathway. PI3K/Akt is an important intracellular signal pathway responsible for cellular processes like cell growth, proliferation and glucose metabolism(38). Binding of the IGF-I to IGF-IR results in the phosphorylation of PI3. PI3 then further activates the Akt pathway, resulting in the phosphorylation of several downstream targets, including the proapoptotic Bad protein and nuclear factor (NF) κB, thus effectively blocking apoptosis and up-regulate cellular survival signal pathways(39,40).

PI3K/Akt also promotes protein synthesis and cell growth through activation of mammalian target of rapamycin (mTOR). mTOR is a conserved Ser/Thr kinase, which regulates cell growth and metabolism and been demonstrated to play an important role in the carcinogenesis of many cancers recently(40). In addition, IGF-I also induces the activation of the Ras/Raf/mitogen-activated-protein-kinase (MAPK) pathway, which mainly increases cellular proliferation via downstream target protein (38). Recent studies suggested that, other factors, altered in obesity, including increased levels of blood insulin, leptin, TNFα, IL-6 as well as decreased adiponectin may all increase the activity of the PI3K/Akt signal pathway, in turn leading to carcinogenesis(4).

Recent study has suggested an autocrine and paracrine loop of IGF system existing in GBC tumor cells (41). By investigating the expression of IGF-I, IGF-II, and IGF-IR in 57 gallbladder carcinoma, corresponding lymph node and hepatic metastases, the analysis showed that IGF-I, IGF-II, and IGF-IR was presented in 55 of 57 primary tumors and 17 of 18 metastases. IGF system seems to be involved at an early stage during carcinogenesis and the IGF-IR staining which intensity decreased significantly with tumor cell dedifferentiation was an independent marker of poor prognosis. Another study found IGF-I and IGF-IR expression in all four human cholangiocarcinoma cell lines, whereas cholangiocytes of intrahepatic bile ducts of normal human liver were all negative(42).

Oxidative stress is another important mechanism in cancer development. Hyperinsulinemia and insulin

resistance have been showed to increase oxidative stress in various tissues (43). Oxidative stress may damage the cholecystokinin (CCK) receptor, thereby causing dysfunctional contractility of gallbladder (44). Increased oxidative stress has been observed in subjects with low high-density lipoprotein (HDL) cholesterol, elevated triglycerides, and central adiposity, all of which were found to be positively associated with gallbladder disease risk (45).

5.2. Gallstone is an established risk factor for GBC

Cholelithiasis is the most commonly recognized risk factor for GBC: more than 95% of GBC cases are associated with gall stones (10, 46). According to a population-based study in China, subjects with non-familial gallstones (i.e., gallstones without a family history) had a 21-fold risk of GBC, whereas those with gallstones and a positive family history had a 57-fold risk of developing GBC (21). Other studies have showed that individuals who develop gallstones are four times (95% CI, 1.5-11) more likely to develop GBC at a younger age (approximately 6 years earlier) than those without gallstones (47). One of the plausible rationales is that the chronic trauma to the gallbladder mucosa caused by gallbladder stones may result in dysplasia and progression to carcinoma (48). This association is especially obvious with the gallstones having earlier initiation or higher growth rate (49). Moreover, there is evidence that patients with gallbladder cancer tended to have more organisms in their bile. Thereby, the presence of infection in the bile is believed to be another risk for stone formation and hence the attendant risk of cancer (50).

Clinically, obesity is an established major risk factor for developing gallstones (45, 51). A recent study from China showed that a BMI of ≥25.0 kg/m2 and triglyceride level of ≥1500 mg/L were significant predictors of gallstone disease in women (52), while in men, gallstones were more related to body shape than to size, and central adiposity and hyperinsulinemia were found to be related to gall stones (53, 54). A Swedish study showed that overweight and obese twins had a significant higher risk for gallstone disease compared with normal BMI twins (OR=1.86 and OR=3.38, respectively) (46). Formation of gallstone is mechanistically related to impaired gallbladder motility, Bile composition (supersaturation with cholesterol), inflammation, hypersecretion of mucin gel in the gallbladder, slow large intestinal motility, and increased intestinal cholesterol absorption, all of which are closely related with obesity and hyperinsulinemia (55).

Hyperinsulinemia, as observed in the insulin resistant state may cause increased hepatic cholesterol secretion and cholesterol supersaturation by stimulating very low-density lipoprotein (VLDL)-triglyceride synthesis and activating hydroxymethylglutaryl coenzyme A reductase (56). Studies have shown that, in overweight subjects with insulin resistance, greater amounts of FFAs are taken up by the liver, more VLDL and cholesterol is produced and secreted (49). Triglyceride (TG) and bile acid

metabolism are linked. There is an inverse relationship between bile acid fluxes and pool size and VLDL production. Over production of cholesterol accompanied with decreasing bile acid fluxes contribute to cholesterol supersaturation in bile (57) thus increase the risk of gallstone. Gallbladder motility is also impaired in obesity patients. Postprandial gallbladder emptying is regulated by CCK. There is evidence that the gallbladder in obesity is less sensitive to CCK causing delayed emptying, which prolongs the residence time of cholesterol in the gallbladder and results in more nucleation and crystallization. The impaired sensitivity shows more obvious in patient with hypertriglyceridemia and will improve after TG lowering therapy (58, 59).

It is well-known that diabetes mellitus (DM) is closely associated with the degree and duration of being overweight or obese. Meanwhile, DM is has been recognized as a predisposing risk factor for GBC (60). In a recent population-based case-control study from Shanghai (61), the relative risk of biliary tract cancer and biliary stones were compared between patients with DM and healthy controls. The study showed that DM was associated with significant risks of GBC (OR=2.6, 95% CI 1.5-4.7) and biliary stones (OR=2.0, 95%CI 1.2-3.3) regardless of BMI. The study also revealed that presence of biliary stones and low serum levels of HDL were significant mediators of the effect of DM on GBC, accounting for 60% and 17% of the DM effect, respectively (61).

5.3. Adipokines

Adipose tissue is a highly active endocrine and metabolic organ which is also considered to have the ability to promote tumorigenesis in cancer cells, by increasing cell proliferation, invasive potential and angiogenesis. These actions are thought to be mediated by production of a variety of hormones and adipokines such as adiponectin, leptin, plasminogen activator inhibitor (PAI)-1, vascular endothelial growth factor (VEGF), TNFα, and interleukin (IL)-6 (7, 33). The most abundant and well-known ones are leptin and adiponectin. Serum leptin level is directly affected by white adipose tissue mass and positively correlates to obesity. Evidence suggests that leptin has several actions, including stimulation growth, migration and invasion in tumor cell models, which may all play a role in tumor development and progression (62). Continuous stimulation of leptin receptors by a high concentration of leptin in chronic obesity can result in leptin resistance. Leptin deficient and leptin-receptor deficient mice show higher body fat content, hyperphagia, hyperglycemia, abnormal reproductive functions, hormonal imbalances and decreased immune function (63). Studies demonstrated that both leptin-deficient and leptin-resistant mice, as well as non-obese diabetic mice, have enlarged gallbladder volumes and decreased gallbladder contractility and that leptin administration to these mice normalizes gallbladder function (64). It is believed that that leptin increases biliary lipid secretion and effect gallbladder dysmotility thus promotes the formation of gallstone (65).

Adiponectin is another important Adipokines secreted mainly from visceral fat adipocytes which is

inversely correlated with BMI. It is an insulin-sensitizing agent and is has significant anti-inflammatory and anti-angiogenic effects (33). Report has demonstrated that hypoadiponectinemia is associated with cholesterol gallstone in human (66). Hypoadiponectinemia might be involved in the occurrence of gallstone disease.

TNFα is over expressed in adipose tissue of obese mice related to insulin resistance (67). TNFα has been shown to promote the survival of cancer cells and chronic stimulation of TNFα may be carcinogenic (68). Adiponectin has been shown to reduce TNFα secretion by macrophages, while leptin has the opposite effect via increasing TNFα production and activation by macrophages (69).

5.4. Sex hormones and GBC

Experimental and clinical evidence have indicated that oestrogens and progesterone can regulate cellular differentiation, stimulate proliferation and inhibit apoptosis, all of these effects may enhance the potential for cancer development (29, 70). Clinical epidemiology data suggest that GBC occurs more commonly in females than in males, indicating that sex hormone may play a role in the development of GBC. A prospective case-control study involving 78 cases of GBC and 78 matched controls showed a higher GBC incidence among females than males (71).

Obesity has been known to be associated with several abnormalities of sex steroid balance. First, adipose tissue expresses various sex-steroid-metabolizing enzymes that promote the formation of oestrogens from androgenic precursors (secreted by the gonads or adrenal glands). Second, excess insulin and bioactive IGF-I in circulation associated with abdominal obesity may suppress sex hormone-binding globulin (SHBG) and stimulate steroidogenesis, leading to increased functional androgen levels and excessive unregulated bioavailable estrogen production from the granulosa cells of the ovaries (72). The increased production and excess presence of unregulated bioavailable estrogen favor the malignant transformation.

Overweight and obese women frequently experience the early onset of puberty and are more likely to have menstrual disturbance such as abnormal and long cycles, heavy menstrual flow and hirsutism (73, 51). Early menarche, higher number of pregnancies and prolonged fertility have all been suggested as risk factors for GBC (49).

Overall, female hormone appears to be a predisposing factor for the development of GBC.

5.5. Fatty infiltration in gallbladder may predispose to GBC

Obesity may lead to fatty infiltration in multiple internal organs. Increased fat deposition contributes to up-regulations of inflammatory mediators such as TNFα, interleukin-6 (IL-6) and C-reactive protein (CRP), resulting

in chronic inflammation and tissue damage (74). Adipose tissue, particularly visceral tissue, is a source of cytokines with serum leptin and IL-6 correlating well with increasing BMI. Increased CRP levels in obese individuals suggest that obesity may be a marker of an escalating immune response. Changes in the levels of cytokines, chemokines, and activation of leukocytes have profound effects on organ structure and function (75).

Increasing evidence has indicated that obesity is inevitably associated with fatty infiltration of the gallbladder, which results in lipotoxic cholecystopathy or fatty gallbladder disease (76). Increased fat deposition in gallbladder may enhance chronic local inflammation, leading to an abnormal wall structure and decreased contractility (77). A recent study in mice suggested that both obesity and dietary carbohydrates increase gallbladder total fat, triglycerides, cholesterol, IL-1β, and TNFα. However, the potential consequences of chronic inflammation in steatocholecystitis on epithelial cell dysplasia in gallbladder have not been investigated (78). It can be postulated that increased inflammatory activity in gallbladder as a consequence of obesity would create a microenvironment that favors epithelial cell transformation. (Figure 2)

6. LIFESTYLE MODIFICATION AS A MEASURE OF PREVENTING GBC IN OBESE PEOPLE

Data from Association for International Cancer Research (AICR) and the World Cancer Research Fund (WCRF) have demonstrated that achievable dietary practices could prevent up to 40% of world cancer cases (79). As discussed above, formation of GBC involves a complex interaction between many factors. Overweight and obesity have been proved to be among the strongest risk factors for GBC (35). Thus, we can conceivably believe that assuming a healthy life style would be a useful approach for reducing the incidence of GBC. Indeed, protective effects of caloric restriction, increased physical activity, use of fresh vegetables, fruits and high fiber diet have been observed to reduce the incidence of many cancers including GBC (35, 80). In addition, more exposure to green space will prevent overweight especially among young people living in high population densities (81).

7. CONCLUSIONS

The incidence of obesity has risen considerably over the recent years. A greater public awareness of the potential health threat associated with obesity is clearly needed, as obesity predisposes to many health problems including insulin resistance, diabetes mellitus, heart disease, dyslipidemia, and more importantly, increased cancer incidence. Obesity leads to supersaturation of cholesterol and poor gallbladder emptying, thus facilitating gallstones formation and GBC. In addition, obesity-related multiple metabolic disorders such as hyperinsulinemia, insulin resistance and hyperlipemia may decrease the sensitivity to CCK, reduce gallbladder contraction, and disturb sex steroid balance. All these factors may
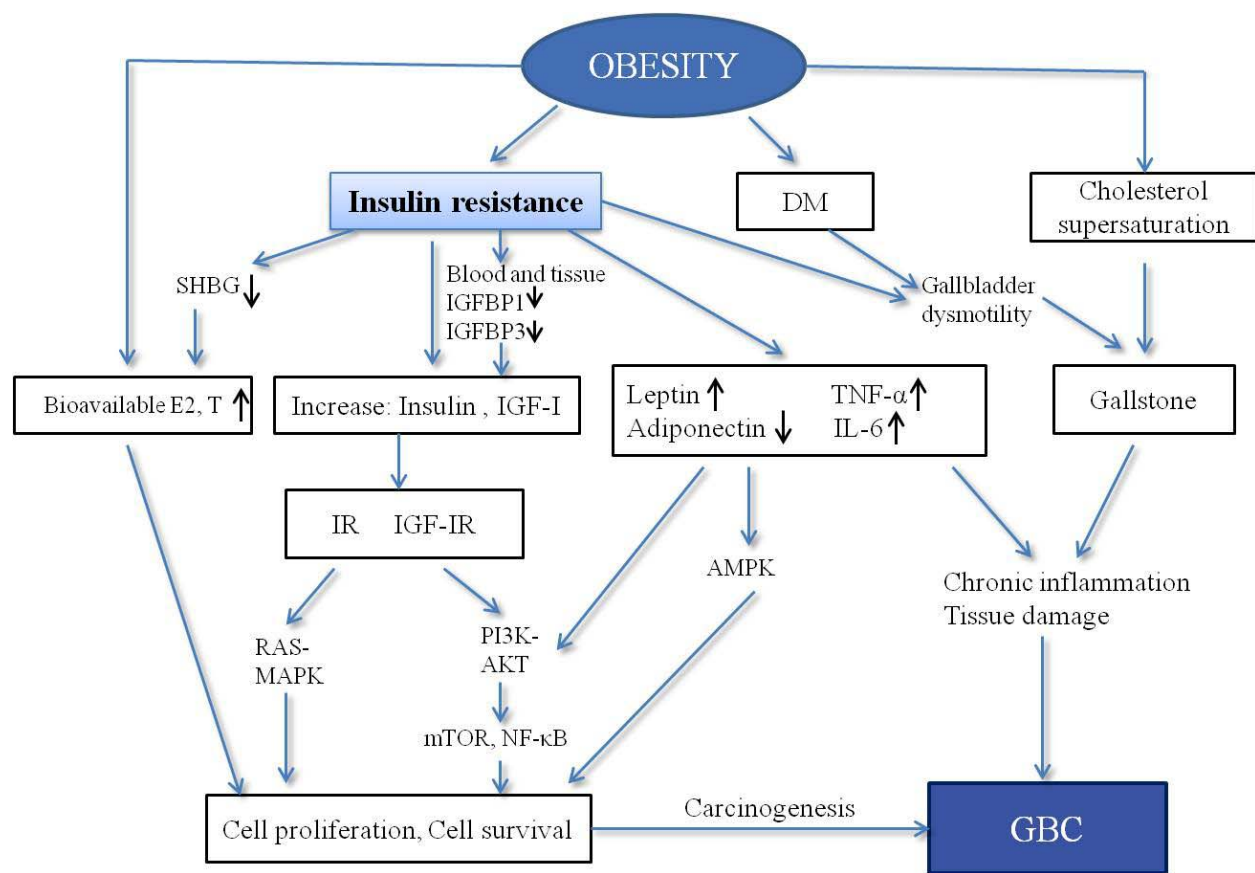
Figure 2. Insulin resistance develops as a metabolic adaptation to increased circulating levels of free fatty acids (FFAs) and is compensated by increased pancreatic insulin secretion, leading to hyperinsulinemia. Chronic hyperinsulinemia reduces the hepatic production of IGFBP-1 and IGFBP-3, resulting in more unbound IGF-I that is free to interact with IGF-IR and increased quantity of bioavailable IGF-I. Insulin and IGF-I signal through binding to the insulin receptors (IRs) and IGF-IR, respectively, promote cellular proliferation and inhibit apoptosis in many tissue types by activating downstream receptors such as PI3K-Akt and MAPK intracellular signal networks. Other factors altered in obesity including increased levels of blood insulin, leptin, TNFα, IL-6, as well as decreased adiponectin, may all increase the activity of the PI3K/Akt signal pathway. These changes may facilitate carcinogenesis. In parallel, insulin resistance especially that associated with abdominal obesity may suppress sex hormone-binding globulin (SHBG) and stimulate steroidogenesis. Hyperinsulinemia may cause increased hepatic cholesterol secretion and cholesterol supersaturation, which in turn, contribute to gallstone formation. Chronic injury to the gallbladder mucosa caused by gallbladder stones and inflammatory mediators may result in dysplasia and progression to carcinoma.

predispose a malignant transformation of gallbladder epithelial cells. Diet, exercise, and other lifestyle modifications are logical steps for controlling obesity and hopefully, reducing the risk of GBC.

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